CJC

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 7,045,518	)	Serial No. 10/677,729
	)	
Inventor(s): Daniel P. GETMAN *et al*	)	Filed: October 3, 2003
	)	
Issue Date: May 16, 2006	)	Attorney Docket No. 101765.00010

For: SULFONYLALKANOYLAMINO HYDROXYETHYLAMINO SULFONAMIDE RETROVIRAL PROTEASE INHIBITORS

REQUEST FOR CERTIFICATE OF CORRECTION

U.S. Patent and Trademark Office
Customer Service Window
Randolph Building, Mail Stop: Certificate of Correction Branch
401 Dulany Street
Alexandria, VA 22314

Sir:

Pursuant to 35 U.S.C. § 254 and 37 C.F.R. § 1.322, this is a request for the issuance of a Certificate of Correction in the above-identified patent. Two (2) copies of PTO Form 1050 are appended. The complete Certificate of Correction involves one page.

The mistakes identified in the appended Form occurred through no fault of the Applicants, as clearly disclosed by the records of the application, which matured into this patent. Enclosed for your convenience is the Amendment filed September 12, 2005 and the initialed Information Disclosure Statement returned with the Office Action dated June 10, 2005.

Issuance of the Certificate of Correction containing the corrections is respectfully requested. Since these changes are necessitated through no fault of the Applicants, no fee is believed to be associated with this request. Nonetheless, should the Patent and Trademark Office determine that a fee is required, please charge our Deposit Account No. 19-0733.

Respectfully submitted,

BANNER & WITCOFF, LTD.

Dated: August 31, 2006

By: _____
Joseph M. Skerpon
Registration No. 29,864

1001 G Street, N.W. (11th Fl.)
Washington, D.C. 20001
(202) 824-3000

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.: 7,045,518

DATED: May 16, 2006

INVENTOR(S): Daniel P. GETMAN *et al*

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the cover page, Related U.S. Application Data section (63):

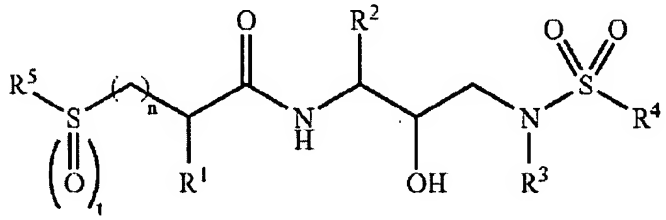
After "5,985,870" please insert --which claims priority to U.S. Serial No. 08/478,625, filed June 7, 1995, now U.S. Patent 5,705,500, which is a continuation-in-part of U.S. Serial No. 08/401,838, filed March 10, 1995, now abandoned.--

On the cover page, References Cited section (56), U.S. Patent Documents:

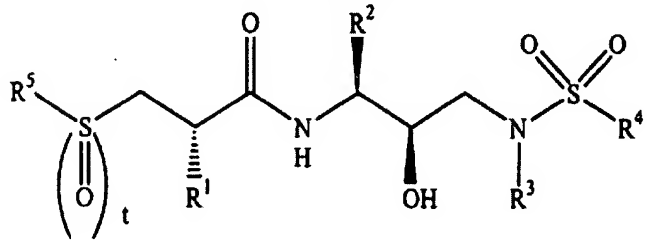
Please insert the following reference: --4,893,530 1/1991 Hemmi et al--

In Column 116, Claim 1, Lines 20-25:

Please replace the following formula:



With the formula presented below:



In Column 117, Claim 2, Line 38:

Please replace "salt," with --salt--

In Column 118, Claim 3, Line 52:

Please replace "benzotbiazol-6-yl" with --benzothiazol-6-yl--

Mailing Address of Sender:

Banner & Witcoff, Ltd.
11th Floor
1001 G Street, N.W.
Washington, DC 20001-4597

U.S. PAT. NO 7,045,518

No. of add'l copies
@ $0.50 per page

☐

FORM PTO 1050 (Rev.2-93)

SEP 05

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.: 7,045,518

DATED: May 16, 2006

INVENTOR(S): Daniel P. GETMAN *et al*

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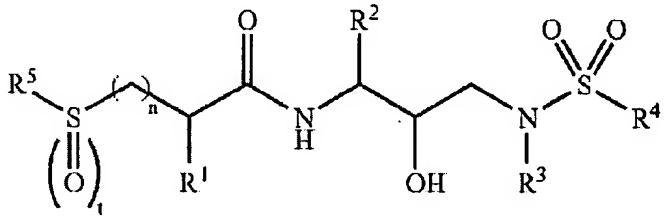
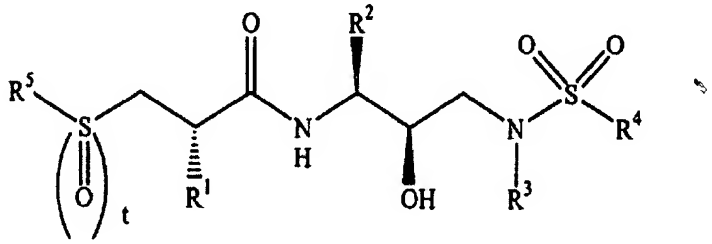


With the formula presented below:



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Please replace "benzotbiazol-6-yl" with --benzothiazol-6-yl--

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1001 G Street, N.W.
Washington, DC 20001-4597

No. of add'l copies
@ $0.50 per page

☐

FORM PTO 1050 (Rev.2-93)

IW

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	
Daniel P. GETMAN *et al.*	Group Art Unit: 1626
Serial No. 10/677,729	Examiner: Powers, F.
Filed: October 3, 2003	Atty. Docket 101765.00010 (2869/6)

For: SULFONYLALKANOYLAMINO HYDROXYETHYLAMINO SULFONAMIDE RETROVIRAL PROTEASE INHIBITORS

AMENDMENT AND RESPONSE UNDER 37 C.F.R. § 1.111

U.S. Patent and Trademark Office
Customer Service Window, Mail Stop Amendment
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir:

In response to the Office Action mailed June 10, 2005, Applicants respectfully request entry of this paper into the file of the above-captioned application. It is believed that a fee of $130 (for the filing of the Terminal Disclaimer accompanying this response) is due. Please charge our deposit account No. 19-0733 for that amount. However, should any additional fees be required or an overpayment of fees made, please debit or credit our Deposit Account No. 19-0733, accordingly.

An AMENDMENTS TO THE SPECIFICATION section begins on page 2 of this paper.

A LISTING OF CLAIMS reflects claim amendments and begins on page 3 of this paper.

A REMARKS section begins on page 11 of this paper.

A Joint Supplemental Declaration and a Terminal Disclaimer under 37 C.F.R. § 1.321(c) accompany this response.

AMENDMENTS TO THE SPECIFICATION

Immediately after the Title, please replace (1) the section heading "RELATED CASE," in the originally-filed application and (2) the first paragraph of the specification, which was inserted in the Preliminary Amendment filed October 3, 2003, with the following section heading and paragraph:

-- ~~RELATED CASE~~

CROSS-REFERENCE TO RELATED APPLICATIONS

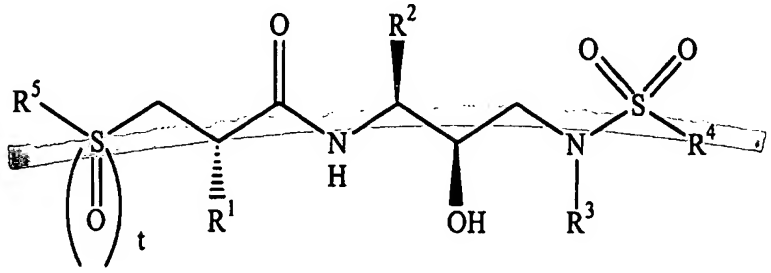
This application is a continuation of U.S. Serial No. 10/082,123 filed February 26, 2002, now U.S. Patent No. 6,667,307, which is a continuation of U.S. Serial No. 09/672,449 filed September 29, 2000 (now U.S.P. 6,380,188); which is a continuation of 09/411,374 filed October 4, 1999 (now U.S.P. ~~6,169,005~~ 6,169,085); which is a continuation of 08/913,069 filed December 19, 1997 (now U.S.P. 5,985,870); which was the national stage entry of PCT/US96/02682, filed March 7, 1996 which claims priority to U.S. Serial No. 08/478,625, filed June 7, 1995, now U.S. Patent 5,705,500, which was a continuation-in-part of U.S. Serial No. 08/401,838, filed March 10, 1995, now abandoned. --

SEP 05 2006

This Listing of Claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS

Claim 1 (currently amended) Compound represented by the formula:



or a pharmaceutically acceptable salt~~, prodrug or ester~~ thereof, wherein t represents 0, 1 or 2;

R^1 represents hydrogen, alkyl of 1-5 carbon atoms, alkenyl of 2-5 carbon atoms, alkynyl of 2-5 carbon atoms, hydroxyalkyl of 1-3 carbon atoms, alkoxyalkyl of 1-3 alkyl and 1-3 alkoxy carbon atoms, cyanoalkyl of 1-3 alkyl carbon atoms, $-CH_2CONH_2$, $-CH_2CH_2CONH_2$, - $CH_2S(O)_2NH_2$, $-CH_2SCH_3$, $-CH_2S(O)CH_3$ or $-CH_2S(O)_2CH_3$ radicals;

R^2 represents radicals of alkyl of 1-5 carbon atoms, aralkyl of 1-3 alkyl carbon atoms, alkylthioalkyl of 1-3 alkyl carbon atoms, arylthioalkyl of 1-3 alkyl carbon atoms or cyloalkylalkyl of 1-3 alkyl carbon atoms and 3-6 ring member carbon atoms;

R^3 represents radicals of alkyl radical of 1-5 carbon atoms, cyloalkyl of 5-8 ring members or cycloalkylmethyl radical of 3-6 ring members;

R^4 represents benzo fused 5 to 6 ring member heteroaryl or benzo fused 5 to 6 ring member heterocyclo radicals, or a radical of the formula

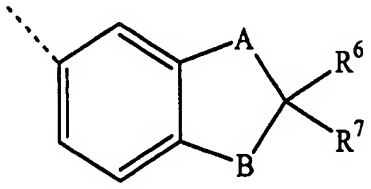
Claim 12 (currently amended) Compound of claim 1, or a pharmaceutically acceptable salt~~, prodrug or ester~~ thereof, wherein t represents 1 or 2;

R^1 represents hydrogen radical, alkyl radical of 1-3 carbon atoms, alkenyl radical of 2-3 carbon atoms, alkynyl radical of 2-3 carbon atoms radicals or cyanomethyl;

R^2 represents radicals of alkyl of 3-5 carbon atoms, arylmethyl, alkylthioalkyl of 1-3 alkyl carbon atoms, arylthiomethyl or cyloalkylmethyl of 5-6 ring member carbon atoms radicals;

R^3 represents alkyl of 1-5 carbon atoms, cyloalkylmethyl of 3-6 ring members, cyclohexyl or cycloheptyl radicals;

R^4 represents 2-amino-benzothiazol-5-yl, 2-amino-benzothiazol-6-yl, benzothiazol-5-yl, benzothiazol-6-yl, benzoxazol-5-yl, 2,3-dihydrobenzofuran-5-yl, benzofuran-5-yl, 1,3-benzodioxol-5-yl or 1,4-benzodioxan-6-yl radicals; or a radical of the formula



wherein A and B each represent O; R^6 represents deuterium, methyl, ethyl, propyl, isopropyl or fluoro radicals; and R^7 represents hydrogen, deuterium, methyl or fluoro radicals; or a radical of the formula

R^{22} represents alkyl radical of 1 to 3 carbon atoms; and

R^5 represents an alkyl radical of 1-5 carbon atoms, alkenyl radical of 3-4 carbon atoms, alkynyl radical of 3-4 carbon atoms or aryl substituted alkyl radical of 1-4 carbon atoms.

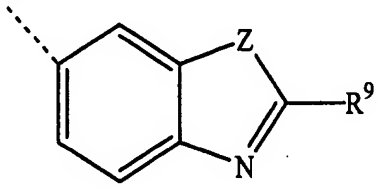
Claim 13 (currently amended) Compound of claim 12, or a pharmaceutically acceptable salt~~, prodrug or ester~~ thereof, wherein

R^1 represents hydrogen, methyl, ethyl or cyanomethyl radicals;

R^2 represents isobutyl, n-butyl, $CH_3SCH_2CH_2$-, phenylthiomethyl, (2-naphthylthio)methyl, benzyl, 4-methoxyphenylmethyl, 4-hydroxyphenylmethyl, 4-fluorophenylmethyl or cyclohexylmethyl radicals;

R^3 represents propyl, isoamyl, isobutyl, butyl, cyclohexyl, cycloheptyl, cylopentylmethyl or cyclohexylmethyl radicals; and

R^4 represents benzothiazol-5-yl, benzothiazol-6-yl, benzoxazol-5-yl, 2,3-dihydrobenzofuran-5-yl, benzofuran-5-yl, 1,3-benzodioxol-5-yl, 2-methyl-1,3-benzodioxol-5-yl, 2,2-dimethyl-1,3-benzodioxol-5-yl, 2,2-dideutero-1,3-benzodioxol-5-yl, 2,2-difluoro-1,3-benzodioxol-5-yl or 1,4-benzodioxan-6-yl radicals; or a radical of the formula



wherein Z represents O, S or NH; and R^9 represents a radical of formula

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,729	10/03/2003	Daniel P. Getman	101765.00010	4872

22907 7590 06/10/2005

BANNER & WITCOFF
1001 G STREET N W
SUITE 1100
WASHINGTON, DC 20001

EXAMINER	
POWERS, FIONA	
ART UNIT	**PAPER NUMBER**
1626	

DATE MAILED: 06/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/677,729	GETMAN ET AL
	Examiner	Art Unit
	Fiona T. Powers	1626

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 12-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 12-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/3/03, 9/1/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

10/677,729

USPTO Form 1449 — U.S. Department of Commerce, Patent and Trademark Office

INFORMATION DISCLOSURE CITATION

Sheet 2 of

Attorney Docket No:	Serial No.:
101765.00010 (2869/6/)	TBA
Applicant(s): GETMAN ET AL.	
Filing Date: 10/03/03	Group: TBA

U.S. PATENT DOCUMENTS

Examiner Initial		Patent No.	Date	Name	Class	Subclass	Filing Date (if appropriate)
FTP	AU	4,634,465	1/1987	Ehrenfreund et al.	71	91	
	AV	4,668,769	5/1987	Hoover	530	331	
	AW	4,668,770	5/1987	Boger et al.	530	331	
	AX	4,757,050	7/1988	Natarajan et al.	514	18	
	AY	4,880,938	11/1989	Freidinger	548	492	
	AZ	4,977,277	12/1990	Rosenberg et al.	549	215	
FTP	BA	4,893,530	1/1991	Hemmi et al.	514	19	

FOREIGN PATENT DOCUMENTS

Examiner Initial					Class	Subclass	Translation YES	Translation NO
FTP	BB	0 337 714	10/1989	EPO				
	BC	0 346 847	12/1989	EPO				
	BD	0 356 223	2/1990	EPO				
	BE	0 389 898	10/1990	EPO				
	BF	0 393 445	10/1990	EPO				
FTP	BG	0 393 457	10/1990	EPO				

OTHER DOCUMENTS (including Author, Title, Date, Pertinent Pages, etc.)

FTP	BH	McQuade et al., *Science*, 274, 454 (1990).
	BI	Rich et al., Pept. Struct. Funct. Am. Pept. Sym. 8th ed. pp. 511-520 (1983).
	BJ	Rosenberg et al., *J. Med. Chem.*, 30, 1224-1228 (1987).
	BK	Fittkau, *J. Prakt. Chem.* 315, 1037 (1973).
	BL	Hirsh et al., *N. Eng. J. Med.*, 328, 1686 (1993).
	BM	E. E. Gilbert, "Recent Developments in Preparative Sulfonation and Sulfation," *Synthesis*, 3 (1969)
FTP	BN	Mitsuya et al., *Proc. Natl. Acad. Sci. USA*, 83, 1911-15 (1986).

EXAMINER Fiona T. Powers — DATE CONSIDERED 6/8/05

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

**Copies of references not provided at the time of this submission.

SEP 05

101765.com June 8, 2006

US007045518B2

(12) **United States Patent**
Getman et al.

(10) **Patent No.: US 7,045,518 B2**
(45) **Date of Patent: *May 16, 2006**

(54) **SULFONYLALKANOYLAMINO HYDROXYETHYLAMINO SULFONAMIDE RETROVIRAL PROTEASE INHIBITORS**

(75) Inventors: **Daniel P. Getman**, Chesterfield, MO (US); **Gary A. DeCrescenzo**, St. Charles, MO (US); **John N. Freskos**, Clayton, MO (US); **Michael L. Vazquez**, Gurnee, IL (US); **James A. Sikorski**, Des Peres, MO (US); **Balekudru Devadas**, Chesterfield, MO (US); **Srinivasan Raj Nagarajan**, Chesterfield, MO (US); **Joseph J. McDonald**, Ballwin, MO (US)

(73) Assignee: **G.D. Searle & Co.**, Chicago, IL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 187 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/677,729**

(22) Filed: **Oct. 3, 2003**

(65) **Prior Publication Data**

US 2004/0147758 A1 Jul. 29, 2004

Related U.S. Application Data

(63) Continuation of application No. 10/082,123, filed on Feb. 26, 2002, now Pat. No. 6,667,307, which is a continuation of application No. 09/672,449, filed on Sep. 29, 2000, now Pat. No. 6,380,188, which is a continuation of application No. 09/411,374, filed on Oct. 4, 1999, now Pat. No. 6,169,085, which is a continuation of application No. 08/913,069, filed as application No. PCT/US96/02682 on Mar. 7, 1996, now Pat. No. 5,985,870. → 08/478,695 filed 6/7/95, now 5,705,500 → 08/401,858, filed 3/10/95, now abandoned

(51) **Int. Cl.**

A61K 31/343	(2006.01)
A61K 31/357	(2006.01)
A61K 31/428	(2006.01)
C07D 277/62	(2006.01)
C07D 317/62	(2006.01)

(52) **U.S. Cl.** **514/228.2**; 514/367; 514/375; 514/464; 514/469; 544/135; 544/137; 546/196; 546/198; 548/178; 548/217; 548/517; 548/518; 549/434; 549/438; 549/467

(58) **Field of Classification Search** 514/228.2, 514/367, 375, 464, 469; 544/135, 137; 546/196, 546/198; 548/178, 217, 517, 518; 549/434, 549/438, 467

See application file for complete search history.

(56) **References Cited**

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-4,477,441	A	10/1984	Boger et al.	424/177
-4,514,391	A	4/1985	Gordon et al.	514/2
-4,548,926	A	10/1985	Matsueda et al.	514/19
-4,595,407	A	6/1986	Carter	71/90
-4,599,198	A	7/1986	Hoover	260/998.2
-4,616,088	A	10/1986	Ryono et al.	546/336
-4,634,465	A	1/1987	Ehrenfreund et al.	71/91
-4,668,769	A	5/1987	Hoover	530/331
-4,668,770	A	5/1987	Boger et al.	530/331
-4,757,050	A	7/1988	Natarajan et al.	514/18
-4,880,938	A	11/1989	Freidinger	548/492
-H725	H	1/1990	Gordon	548/533
4,963,530	A	10/1990	Hemmi et al.	514/19
-4,977,277	A	12/1990	Rosenberg et al.	549/215
-5,705,500	A	1/1998	Getman et al.	
-5,985,870	A	11/1999	Getman et al.	
-6,169,085	B1	1/2001	Getman et al.	
-6,380,188	B1	4/2002	Getman et al.	
-6,667,307	B1	12/2003	Getman et al.	

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-EP	0 104 041	3/1984
-EP	0 114 993	8/1984
-EP	0 172 347	2/1986
-EP	0 223 437	5/1987
-EP	0 264 795	4/1988
-EP	0 342 541	5/1989
-EP	0 337 714	10/1989
-EP	0 346 847	12/1989
-EP	0 356 223	2/1990
-EP	0 389 898	10/1990
-EP	0 393 445	10/1990
-EP	0 393 457	10/1990
-EP	0 402 646	12/1990
-EP	0 468 641	1/1992
-GB	2184730	7/1987
-GB	2200115	7/1988
-GB	2209752	5/1989
-WO	84/03044	8/1984

(Continued)

OTHER PUBLICATIONS

International Search Report of PCT/US96/02682 dated Aug. 21, 1996.

(Continued)

Primary Examiner—Fiona T. Powers
(74) *Attorney, Agent, or Firm*—Banner & Witcoff, Ltd.

(57) **ABSTRACT**

Selected sulfonylalkanoylamino hydroxyethylamine sulfonamide compounds are effective as retroviral protease inhibitors, and in particular as inhibitors of HIV protease. The present invention relates to such retroviral protease inhibitors and, more particularly, relates to selected novel compounds, composition and method for inhibiting retroviral proteases, such as human immunodeficiency virus (HIV) protease, prophylactically preventing retroviral infection or the spread of a retrovirus, and treatment of a retroviral infection.

7 Claims, No Drawings

SEP 05

FOREIGN PATENT DOCUMENTS

WO	WO 92/00750	1/1992
WO	92/08699	5/1992
WO	93/13066	7/1993
WO	94/04493	3/1994
WO	94/08458	5/1994
WO	94/10136	5/1994
WO	WO 95 06030	3/1995
WO	WO 95 33464	12/1995

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The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore may deviate from the preferred dosage regimen set forth above.

The compounds of the present invention may be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

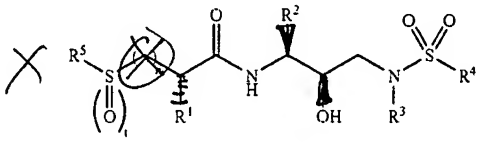
While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more immunomodulators, antiviral agents or other antiinfective agents. For example, the compounds of the invention can be administered in combination with AZT, DDI, -DDC or with glucosidase inhibitors, such as N-butyl-1-deoxynojirimycin or prodrugs thereof, for the prophylaxis and/or treatment of AIDS. When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

1. Compound represented by the formula:



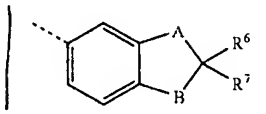
or a pharmaceutically acceptable salt thereof, wherein t represents 0, 1 or 2;

R^1 represents hydrogen, alkyl of 1–5 carbon atoms, alkenyl of 2–5 carbon atoms, alkynyl of 2–5 carbon atoms, hydroxyalkyl of 1–3 carbon atoms, alkoxyalkyl of 1–3 alkyl and 1–3 alkoxy carbon atoms, cyanoalkyl of 1–3 alkyl carbon atoms, —CH_2CONH_2, —$CH_2CH_2CONH_2$, —$CH_2S(O)_2NH_2$, —CH_2SCH_3, —$CH_2S(O)CH_3$ or —$CH_2S(O)_2CH_3$ radicals;

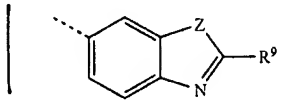
R^2 represents radicals of alkyl of 1–5 carbon atoms, aralkyl of 1-3 alkyl carbon atoms, alkylthioalkyl of 1-3 alkyl carbon atoms, arylthioalkyl of 1–3 alkyl carbon atoms or cyloalkylalkyl of 1–3 alkyl carbon atoms and 3–6 ring member carbon atoms;

R^3 represents radicals of alkyl radical of 1–5 carbon atoms, cyloalkyl of 5–8 ring members or cycloalkylmethyl radical of 3–6 ring members;

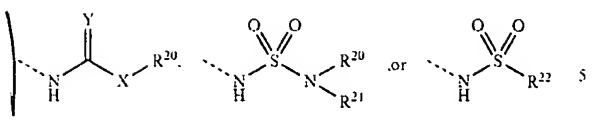
R^4 represents benzo fused 5 to 6 ring member heteroaryl or benzo fused 5 to 6 ring member heterocyclo radicals, or a radical of the formula



wherein A and B each independently represent O, S, SO or SO_2; R^6 represents deuterium, alkyl of 1-5 carbon atoms, fluoro or chloro radicals; R^7 represents hydrogen, deuterium, methyl, fluoro or chloro radicals; or a radical of the formula



wherein Z represents O, S or NH; and R^9 represents a radical of formula



wherein Y represents O, S or NH; X represents a bond, O or NR^{21};

R^{20} represents hydrogen, alkyl of 1 to 5 carbon atoms, alkenyl of 2 to 5 carbon atoms, alkynyl of 2 to 5 carbon atoms, aralkyl of 1 to 5 alkyl carbon atoms, heteroaralkyl of 5 to 6 ring members and 1 to 5 alkyl carbon atoms, heterocycloalkyl of 5 to 6 ring members and 1 to 5 alkyl carbon atoms, aminoalkyl of 2 to 5 carbon atoms, N-mono-substituted or N,N-disubstituted aminoalkyl of 2 to 5 alkyl carbon atoms wherein said substituents are radicals of alkyl of 1 to 3 carbon atoms, aralkyl of 1 to 3 alkyl carbon atoms radicals, carboxyalkyl of 1 to 5 carbon atoms, alkoxycarbonylalkyl of 1 to 5 alkyl carbon atoms, cyanoalkyl of 1 to 5 carbon atoms or hydroxyalkyl of 2 to 5 carbon atoms;

R^{21} represents hydrogen radical or alkyl radical of 1 to 3 carbon atoms; or the radical of formula $—NR^{20}R^{21}$ represents a 5 to 6 ring member heterocyclo radical; and

R^{22} represents alkyl radical of 1 to 3 carbon atoms or $R^{20}R^{21}N$-alkyl radical of 1 to 3 alkyl carbon atoms; and

R^5 represents an alkyl radical of 1–5 carbon atoms, alkenyl radical of 2–5 carbon atoms, alkynyl radical of 2–5 carbon atoms or aryl substituted alkyl radical of 1–5 carbon atoms.

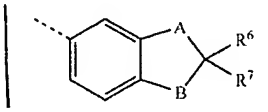
2. Compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein t represents 1 or 2;

R^1 represents hydrogen radical, alkyl radical of 1–3 carbon atoms, alkenyl radical of 2–3 carbon atoms, alkynyl radical of 2–3 carbon atoms radicals or cyanomethyl;

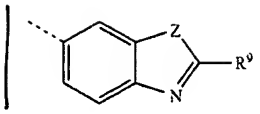
R^2 represents radicals of alkyl of 3–5 carbon atoms, arylmethyl, alkylthioalkyl of 1–3 alkyl carbon atoms, arylthiomethyl or cyloalkylmethyl of 5–6 ring member carbon atoms radicals;

R^3 represents alkyl of 1–5 carbon atoms, cyloalkylmethyl of 3–6 ring members, cyclohexyl or cycloheptyl radicals;

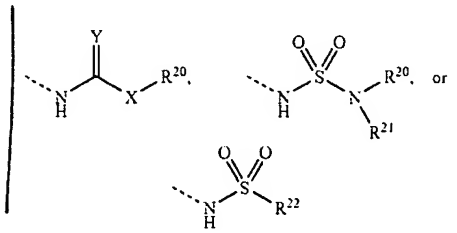
R^4 represents 2-amino-benzothiazol-5-yl, 2-amino-benzothiazol-6-yl, benzothiazol-5-yl, benzothiazol-6-yl, benzoxazol-5-yl, 2,3-dihydrobenzofuran-5-yl, benzofuran-5-yl, 1,3-benzodioxol-5-yl or 1,4-benzodioxan-6-yl radicals; or a radical of the formula



wherein A and B each represent O; R^6 represents deuterium, methyl, ethyl, propyl, isopropyl or fluoro radicals; and R^7 represents hydrogen, deuterium, methyl or fluoro radicals; or a radical of the formula



wherein Z represents O, S or NH; and R^9 represents a radical of formula



wherein Y represents O, S or NH; X represents a bond, O or NR^{21};

R^{20} represent hydrogen, alkyl of 1 to 5 carbon atoms, phenylalkyl of 1 to 3 alkyl carbon atoms, heterocycloalkyl of 5 to 6 ring members and 1 to 3 alkyl carbon atoms, or N-mono-substituted or N,N-disubstituted aminoalkyl of 2 to 3 alkyl carbon atoms wherein said substituents are alkyl radicals of 1 to 3 carbon atoms; and

R^{21} represents hydrogen or methyl radicals; or the radical of formula $—NR^{20}R^{21}$ represents pyrrolidinyl, piperidinyl, piperazinyl, 4-methylpiperazinyl, 4-benzylpiperazinyl, morpholinyl or thiamorpholinyl radicals; and

R^{22} represents alkyl radical of 1 to 3 carbon atoms; and

R^5 represents an alkyl radical of 1–5 carbon atoms, alkenyl radical of 3–4 carbon atoms, alkynyl radical of 3–4 carbon atoms or aryl substituted alkyl radical of 3–4 carbon atoms.

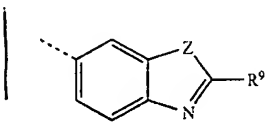
3. Compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein

R^1 represents hydrogen, methyl, ethyl or cyanomethyl radicals;

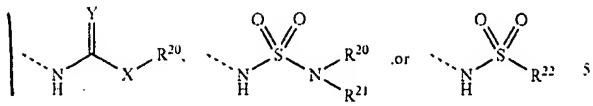
R^2 represents isobutyl, n-butyl, $CH_3SCH_2CH_2—$, phenylthiomethyl, (2-naphthylthio)methyl, benzyl, 4-methoxyphenylmethyl, 4-hydroxyphenylmethyl, 4-fluorophenylmethyl or cyclohexylmethyl radicals;

R^3 represents propyl, isoamyl, isobutyl, butyl, cyclohexyl, cycloheptyl, cylopentylmethyl or cyclohexylmethyl radicals; and

R^4 represents benzothiazol-5-yl, benzothiazol-6-yl, benzoxazol-5-yl, 2,3-dihydrobenzofuran-5-yl, benzofuran-5-yl, 1,3-benzodioxol-5-yl, 2-methyl-1,3-benzodioxol-5-yl, 2,2-dimethyl-1,3-benzodioxol-5-yl, 2,2-dideutero-1,3-benzodioxol-5-yl, 2,2-difluoro-1,3-benzodioxol-5-yl or 1,4-benzodioxan-6-yl radicals; or a radical of the formula



wherein Z represents O, S or NH; and R^9 represents a radical of formula



wherein Y represents O, S or NH; X represents a bond, O or NR^{21};

R^{20} represents hydrogen, methyl, ethyl propyl, isobutyl, benzyl, 2-(1-pyrrolidinyl) ethyl, 2-(1-piperidinyl)ethyl, 2-(1-piperazinyl)ethyl, 2-(4-methylpiperazin-1-yl) ethyl, 2-(1-morpholinyl)ethyl, 2-(1-thiamorpholinyl) ethyl or 2-(N,N-dimethylamino)ethyl radicals;

R^{21} represents a hydrogen radical; and

R^{22} represents methyl radical; and

R^5 represents an alkyl radical of 1–5 carbon atoms or phenyl substituted alkyl radical of 2–4 carbon atoms.

14 4. Compound of claim 3 or a pharmaceutically acceptable salt thereof, wherein

R^1 represents methyl or ethyl radicals;

R^2 represents benzyl, 4-fluorophenylmethyl or cyclo hexylmethyl radicals;

R^4 represents benzothiazol-5-yl, benzothiazol-6-yl, 2,3-dihydrobenzofuran-5-yl, benzofuran-5-yl, 1,3-benzodioxol-5-yl, 2-methyl-1-,3-benzodioxol-5-yl, 2,2-dimethyl-1,3 benzodioxol-5-yl, 2,2-dideutero-1,3-benzodioxol-5-yl, 2,2-difluro-1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 2-(methoxycarbonylamino)benzothiazol-6-yl or 2-(methoxycarbonylamino)benzimidazol-5-yl radicals; and

R^5 represents methyl, ethyl, propyl, isopropyl or 2-phenylethyl radicals.

15 5. Composition comprising a compound of claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

16 6. Method of inhibiting a retroviral protease to treat a retroviral infection or AIDS comprising administering an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

19 7. Method of preventing replication of retrovirus in vitro comprising administering an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

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